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10/039,171	01/03/2002	Robert Haley	UTSD:749US	7156

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EXAMINER	
WHITEMAN, BRIAN A	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/23/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)
	10/039,171	HALEY ET AL.
	Examiner	Art Unit
	Brian Whiteman	1635

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *4/14/05;6/15/05*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35* is/are pending in the application.

4a) Of the above claim(s) *2,28,31-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3-27,29-30,35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *03 January 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/18/02*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Non-Final Rejection

Claims 1-35 are pending.

The amendment to the specification and the updated sequence listing filed on 4/14/05 and 6/15/05 is acknowledged and considered by the examiner.

The letter indicating the claims readable on the elected species filed on 6/15/05 is acknowledged and considered by the examiner.

Election/Restrictions

Applicant's election of Group II (claims 1, 3-27, 29-30, and 35) and the species adenovirus in the reply filed on 4/14/05 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 2, 28, and 31-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention and in herpesviral vector, a retroviral vector, an adeno-associated viral vector, a polyoma viral vector, and a vaccina viral vector in claim 11 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim. Election was made **without** traverse in the reply filed on 4/14/05.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 10/18/02 is being considered by the examiner.

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892 or the IDS filed on 10/18/02, they have not been considered.

Claim Objections

Claim 30 is objected to because of the following informalities: the term "a infectious virus" is grammatically incorrect. Suggest replacing the term with -- an infectious virus --. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 3-27, 29-30, and 35 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of protecting a mouse from an organophosphate comprising administering to the mouse an expression cassette comprising a

promoter operably linked to a gene encoding PON1, wherein the expression of PON1 results in detoxication of the organophosphate, does not reasonably provide enablement for treating or protecting a cell or a subject from a genus of toxins. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Applicants claim a method of treating a subject from a genus of toxins comprising administering an expression cassette comprising a promoter operably linked to a gene encoding PON1. More specifically, the applicants claim either treating or protecting Gulf War Syndrome in a subject or protecting a subject from a chemical warfare agent. Claims 1 and 3-20 can read on a method for in a cell either in vivo or in vitro. The claims are considered broad. With regard to the claimed method practice in vitro, applicant's disclosure does not teach the skilled artisan how to use this method in vitro. The only in vitro embodiment involves testing recombinant adenovirus in 293 cells (page 41). The only disclosed use for transferring and expressing PON1 is for treatment (protecting or treating) of an in vivo cell from a toxin. In view of the guidance in the specification, the claimed methods are directed to a method of gene therapy.

The test of enablement is whether one skilled in the art could make and use the claimed invention from the disclosure in the application coupled with information known in the art without undue experimentation (*United States v. Telectronics, Inc.* 8 USPQ2d 1217 (Fed. Cir. 1988). Whether undue experimentation is required is not based upon a single factor, but rather is a conclusion reached by weighing many factors. These factors were outlined in *Ex parte*

Forman, 230 USPQ 546 (Bd. Pat. App. & Inter. 1986) and again in *In Re Wands* as set forth above.

At the time the application was filed, gene therapy was considered to be unpredictable due to significant problems in several areas. The state of the art, exemplified by Anderson et al., Nature, Vol. 392, pp. 25-30, 1998, displays major consideration for any gene transfer or any DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method.

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, *Nature*, Vol. 389, pages 239-242, 1997, indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2). Thus, at the time the application was filed, the state of the art for gene therapy was considered highly unpredictable.

For additional reviews of the unpredictability of the gene therapy art, see Davis (Curr. Opin. Biotechnol., 2002 3:128-31); Schmidt-Wolf et al. (TRENDS in Molecular Medicine 9:67-72, 2003); Stribley et al. (Fertility and Sterility 77:645-57, 2002).

The instant specification teaches that paraoxonases can hydrolyze organophosphates and protect against such toxicity (page 2). Paraoxonases can act on several organophosphate substrates (page 2). Paraoxonase activity is present in the serum of most mammals as well as in tissue such as the liver, kidney, small intestine (page 3).

Applicants teach the use of recombinant adenovirus comprising a gene encoding either PON1 type R or type Q followed by chlorphyrifos challenge in mice (pages 43-44). The serum paraoxonase activity was higher in the type R treated group compared to the control group. The serum paraoxonase was not significantly different from that of the control group. The mice receiving the adenovirus were protected or partially protected from chlorphyrifos. However, the relevance of this data to protecting a subject from a genus of toxins is unclear at best because

neither the applicant nor the prior art provide a correlation or nexus between the results obtained in in vivo studies such as those provided by applicants with results which the skilled artisan would reasonably expect to see in vivo when the subject is exposed to a genus of toxins. The broadest claims read on a method of protecting a subject against all toxins (chemical warfare agents). However, there are numerous agents or toxins that are not hydrolyzed by PON1. The art of record teaches that oxon metabolites and nerve agents are potent cholinesterase inhibitors (Furlong et al. NeuroToxicology 19:645-650, 1998). However, the genus of toxins (cyanide, chlorine, agent orange, sulphur mustard, lewisite, nitrogen mustard, mustard-leweisite, phosgene-oxime, SN gas, CS gas, etc.) embraced by the claimed method(s) is broader than cholinesterase inhibitors. The invention involves one of the most complex areas of medicine/molecular biology, gene therapy for protecting from toxins in humans. As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed expression cassettes generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices all nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In addition, with respect to treating a genus of subjects using the claimed method, the specification is not considered enabled. The breadth of the claim is considered broad because the claim reads on a genus of subject (including humans, primates, sharks, birds, cats, dogs, mouse, rats, monkeys, insects, farm animals, etc.). The claimed methods read on protecting a subject from exposure of toxin, wherein the subject could be exposed to the toxin, 1 second, 1 minute, 1 hour, 1 day, 1 year, 10 years, etc. The transient nature of gene therapy and the time required for

each vector (viral or non-viral vector) to transfect cells and express the DNA varies is well known to the skilled artisan. The specification does not address these issues. As stated in the specification some subjects express PON1 and some subjects do not express PON1 at all (page 3). In view of the specification, it appears that the main goal of the claimed method is protecting humans exposed to chemical warfare agents. As stated above, the applicants teach expressing human PON1 in mice using an adenovirus comprising a CMV promoter. However, the art of record teaches that although the generating mouse lines that express human PON1 using human cDNA constructs were not successful (Furlong et al., supra). Furlong futher teaches that, "Since the regulatory mechanism of human PON1 expression has not yet been identified, it is unknown whether any cis-acting elements required for PON1 transcription are included in these constructs (page 649)." The art of record and the specification do not teach what amount of toxin is above the level that PON1 can hydrolyze. In view of the history of chemical warfare (WWI, WWII, etc.), the skilled artisan would understand that the goal of chemical warfare is to kill your opponent, which might result in the subject being exposed to a toxin (organophophate) that is above the level that PON1 can hydrolyze. The applicants assert that, at the time of the invention, studies with PON1 gene therapy have not been attempted (page 4). Thus, expressing PON1 in a genus of subjects for protecting the subjects against all toxins (chemical warfare agent) is considered unpredictable.

Furthemore, the specification does not teach the skilled artisan that it would be routine for the skilled artisan to reasonably extrapolate from protecting a murine model exposed to an organophosphate using the recited method to protecting a genus of subjects. The art of record teaches that the extrapolation is considered unpredictable. See United Stated General

Accounting Office: Report to Congressional Requesters, Chemical Weapons DOD Does not have a Strategy to Address Low-Level Exposures September 1998, pages 1-39.

Furthermore, with respect to claim 35 directed to treating or preventing a subject from Gulf War Syndrome, the recited method is not considered enabled. The claimed method reads on using the method to treat a subject that already has Gulf War Syndrome (Symptoms reported include nausea, cramps, rashes, short-term memory loss, fatigue, difficulty in breathing, headaches, joint and muscle pain, birth defects, etc.) and protecting (partial/full protection) a subject from Gulf War Syndrome. The prior art teaches that it is unclear what causes Gulf War Syndrome (Answers.com, Gulf War Syndrome, GuruNet, http://www.answers.com/topic/gulf-war-syndrome, [retrieved on 8/15/05]. Retrieved from: Yahoo.com). The prior art teaches that exposure to organophosphates could be a cause of Gulf War Syndrome (C23-C24). As stated above, the applicants teach protecting a mouse from exposure to an organophosphate. However, the breadth of the claimed method is broader than what is taught by the instant specification. For example, the specification does not teaching using the claimed method to treat subjects that already have Gulf War Syndrome. The specification and the art of record are absent for whether or not the claimed method can reverse the damaged of a subject with a syndrome/symptom associated with Gulf War Syndrome. Thus, to the extent the claim fails to recite distinguishing features to commensurate with the level of guidance presented, the claim is not considered enabled.

In conclusion, the instant specification and claims coupled with the art of record, at the time the invention was made, only provide sufficient guidance and/or evidence to reasonably enable a method of protecting a mouse from an organophosphate comprising administering to the

mouse an expression cassette comprising a promoter operably linked to a gene encoding PON1, wherein the expression of PON1 results in detoxication of the organophosphate and not for the full scope of the claimed invention. Given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any expression cassette cited in the claims, one skilled in the art would have to engage in a large quantity of undue experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 3-20, and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 (and claims dependent therefrom) recites the limitation "said host cell" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Claim 30 recites the limitation "said form suitable for self administration" in line 1. There is insufficient antecedent basis for this limitation in the claim.

Conclusion

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. Claims 1, 6-14, 21-24 and 29 would be anticipated by Hudson et al. (US 5,629,193).

Hudson teaches, "Human serum paraoxonase/arylesterase catalyzes the hydrolysis of organophosphates, aromatic carboxylic acid esters, and carbamates". See column 1. Hudson teaches a process for a polynucleotide encoding Pon1 polypeptide for therapeutic purposes, for example, as an antidote for organophosphate toxicity (pesticide poisoning) and in preventing neuronal cell death (columns 1 and 7). However in view of the unpredictability of gene therapy at the time the application was filed, the teaching of Hudson is not considered enabled because Hudson fails to recite distinguishing features to commensurate with the level of skill required to practice the method.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (571) 272-0764. The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang, acting SPE – Art Unit 1635, can be reached at (571) 272-0811.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

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